REMARKS

Entry of the foregoing and favorable reexamination and reconsideration of the subject application, as amended, pursuant to and consistent with 37 C.F.R. Section 1.112, and in light of the remarks which follow, are respectfully requested.

By the present amendment Claim 1 has been amended to further clarify the molecule. Claims 3 and 5 have been canceled. Applicants reserve their rights to file a continuation application directed to the canceled subject matter. Claim 29 has been added. Applicants submit that no new matter has been added via this amendment.

Prior to specifically addressing the issues brought to bear by the Examiner, Applicants would like to briefly discuss the present invention. The present invention thus relates to a universal polypeptidic carrier for targeting directly or indirectly a molecule to Gb3 receptor expressing cells and having the following formula STxB-Z(n)-Cys, wherein :

STxB is the Shiga Toxin B subunit or a functional equivalent thereof,

Z is an amino-acid devoid of a sulfhydryl group, n being 0, 1 or a polypeptide,

Cys is the amino-acid Cysteine, wherein said molecule is an antigen to be targeted to antigen presenting cells.

Besides the molecule being an antigen, the molecule, as reflected in new Claim 29 can also be selected from the group consisting of proteins, peptides, oligopeptides, glycoproteins, glycopeptides, nucleic acids, polynucleotides, and a combination thereof.

It should be recalled that the Shiga Toxin B subunit has two cysteine residues in the sequence, which form a cysteine bridge. The cysteine bridge is necessary to maintain the configuration of the protein and hence its activity to bind to the Gb3 receptor expressing cells.

The addition of another free cysteine residue to the Shiga B toxin would not be so straightforward; i.e., there would not be any expectation of success that by adding a free cysteine to the Shiga B toxin construct that the protein configuration would be maintained.

For instance, it was known in the art that G-CSF have 5 cysteine residues in which 4 of the cysteines form an intermolecular disulfige bonds and one of the cysteine is a free cysteine in which a disulfide bridge is not formed. The free cysteine in G-CSF leads to molecular instability and intermolecular disulfide scrambling as evidenced in Ishikawa et al (1992) and Bartowoski 2002. Copies of these articles are submitted with the accompanying Information Disclosure Statement. See also Example 8 in U.S. Patent 4,810,643 in which in Example 8 the cysteine residues are replaced with serine residues.

Likewise, like G-CSF, EGF has 6 cysteine residues forming 3 intermolecular disulfide bridges and adding a free cysteine led, in some cases, but not all instances, to intermolecular scrambling, also changing the structure of the protein as evidenced by Lu, 2005. A copy of this reference is also submitted with the Information Disclosure Statement.

Thus, due to the unpredictability of attaching a free cysteine to a protein that must maintain its structural integrity to function effectively, there would be no expectation of success that the protein structure would be maintained such that the universal carrier can target Gb3 expressing cells, enter into the cells and through the MHC class-1 restricted pathway.

Turning now to the Official Action, Claims 1 to 8, 25, 26 and 28 have been rejected under 35 U.S.C. §103 (a) as being unpatentable over Haicheur et al(J. Immunology 2000,

165:3301-3308) in view of Wang et al WO 95/11998) and Eichner (U.S. Patent 5,944,311). For the following reasons, this rejection is respectfully traversed.

Haicheur et al. disclose a fusion protein of a Shiga B toxin fused to a tumor protein from a mouse mastocytoma P815 and further disclose that this fusion protein can induce specific CTL in mice without the use of an adjuvant. It was demonstrated that the B subunit mediates the delivery of various endogenous CD8 T cell epitopes into the conventional MHC class-I restricted pathway via binding to the glycoprotein Gb3.

This fusion protein was constructed by inserting a PCR cassette containing the P815A sequence into the *NotI* site of pB-Gyc-KDEL using specific primers and fusing this sequence to the Shiga B subunit.

Haicheur et al. do not suggest using a cysteine in their construct such that antigens can be presented to antigen presenting cells or that proteins, peptides, oligopeptides, glycoproteins, glycopeptides, nucleic acids, polynucleotides and combinations thereof can be targeted into Gb3 expressing cells. Nor does this reference suggest STxB-Z(n)-Cys where Z is an amino acid devoid of a sulfhydryl group and n is 1 or a polypeptide.

Wang et al. disclose structured synthetic antigen libraries (SSAL) which provide a broad range of sequences that necessitated by the strain or antigenic variation in antigens and hence can simultaneously provide cross-reactivity to multiple strains of an infectious agent. These SSAL can be used as vaccines, therapeutics and in diagnostics. These libraries can between 8 to 100 amino acids. The libraries can be directly or indirectly coupled to carrier proteins such as BSA, HSA, red blood cells or latex particles through a cysteine. These carriers can act as immunogens for antibody production and only circulate the SSAL through the circulation system. They do not have the capacity to enter specific cells themselves via Gb3 presenting cells.

Wang et al does not disclose using the B subunit of Shiga toxin such that various proteins, peptides, oligopeptides, glycoproteins, glycopeptides, nucleic acids and combinations thereof can be targeted into Gb3 presenting cells.

Thus, in Wang et al. there is no need to maintain a specific conformational shape by delivering the SSAL libraries via carriers since the carrier-library constructs are not intended to target GB3 presenting cells, enter the cells and be transported through the MHC class I-restricted pathway.

Eichner et al. disclose adhesion peptides for modifying the adhesion capacity of eukaryotic cells. The peptide sequences have a length of 6 to 30 amino acids or 12 to 14 amino acids. These adhesion peptides can be used to promote cell attachment processes or wound repair processes or to inhibit cell/ cell adhesion of eukaryotic cells. In other words these peptides remain on the exterior of cells, as shown in the Figures.

According to one embodiment, the adhesion peptides can be bound to carriers such as BSA, KLH, ovalbumin, polylysine, lipoproteins, synthetic polymers and the like. The peptides can be coupled by reactivating a reactive group in the molecule such as an amino (NH_2), imino (imidazol ring), hydroxyl (OH), sulphohydryl (SH) or carboxyl (COOH) groups.

There is no suggestion in Eichner et al to use an universal carrier of the subunit of Shiga toxin B such that the Gb3 receptor cells are targeted directly or indirectly having either a cysteine directly attached to the STxB moiety or through a linker Z(n) where Z is an amino acid devoid of a sulfhydryl group, n is 1 or a polypeptide. Eichner et al only teach chemical linkers such as SMCC.

The combination of references fails to render the present invention obvious since there would be no expectation of success that such a universal carrier would in fact maintain its targeting characteristics and the functional biological activity of the molecule that is being

targeted when the construct is not a fusion protein and has a free cysteine. As discussed above this free cysteine was known to result in protein instability and more often than not change the conformational structure thereof.

Indeed Haicheur et a. used a more natural fusion protein such that this fusion protein maintained its natural properties and could in fact retain its targeting and natural properties. Although the secondary references of Wang et al. and Eichner et al. teach linkage through a cysteine to a carrier protein, the carrier protein does not have any receptor function and hence there is no need to maintain its structure to enter the cell with a molecule.

Thus, Applicants submit that the presently claimed invention is not obvious in view of the cited prior art.

Therefore in view of the above, withdrawal of this rejection is respectfully requested.

From the foregoing, favorable action in the form of a Notice of Allowance is respectfully requested and such action is earnestly solicited.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact MaryAnne Armstrong, Ph.D., Reg. No. 40,069 at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

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Respectfully submitted,

By _____

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